The Emergence of Mycophenolate Mofetil in Dermatology

From Its Roots in the World of Organ Transplantation to its Versatile Role in the Dermatology Treatment Room

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Mycophenolate mofetil (MMF) is a "prodrug" of an older predecessor drug, mycophenolic acid (MPA). First isolated as a fermentation product of *Penicillium stoloniferum* cultures by Gozio in 1896, MPA was originally used as a weak organic acid in 1913. This agent received attention due to its antibacterial, antiviral, antifungal, antitumor, and immunosuppressive properties based on data from early studies.[1–6] As for therapeutic application in dermatology, MPA was first used successfully in treating psoriasis in 1975.[7] However, concerns emerged regarding adverse reactions to MPA, most notably gastrointestinal (GI) side effects. GI intolerability coupled with growing concerns regarding the potential long-term risk of carcinogenicity stifled the utilization of MPA, leading to subsequent discontinuation of its use.[8] MPA has since been reformulated as MMF, the semi-synthetic 2-morpholinoethyl ester of MPA. This newer formulation exhibited enhanced bioavailability, greater efficacy, and fewer GI side effects.[9] MMF gained approval by the United States Food and Drug Administration (FDA) in 1995 for the prevention of renal, cardiac, and hepatic allograft rejection.[10–12] Besides use for the FDA-approved indications in organ transplant recipients, MMF soon became recognized as an effective treatment option for several dermatological disorders, necessitating greater attention to dosage regimens, efficacy, safety, monitoring considerations, and drug interactions among dermatologists.

What is the active metabolite of mycophenolate mofetil, and in what patient population does it become sensitive due to its excretion mechanism?

MMF is quickly and completely hydrolyzed by plasma esterases to its parent compound, MPA, after oral or intravenous (IV) administration. Peak concentration of the active metabolite, MPA, is reached within 60 to 90 minutes after oral administration. Oral bioavailability in healthy individuals has been reported to be 94 percent as compared to IV administration.[13,14] MPA is predominantly bound to albumin.

Hepatic conjugation by glucoronyl transferase converts MPA to its principal metabolite, mycophenolic acid glucuronide (MPAG), which is inactive.[15] In addition, two minor metabolites are also formed, 7-O-glucoside and acyl glucuronide, both of which are also clinically inactive.[16] Like MPA, MPAG is highly bound to plasma albumin. Approximately 87 percent of MPA is excreted in urine and six percent in feces, with less than one percent of the administered dose of MMF excreted as the active drug metabolite, MPA.[13] Importantly, patients with renal impairment sustain higher levels of MPA due to decreased renal clearance. Patients with renal impairment may necessitate use of a lower dose and/or closer monitoring.

What is the mechanism of action of immunosuppression related to administration of mycophenolate mofetil?

MMF produces immunosuppression through

inhibition of *de-novo* purine synthesis. Its active metabolite, MPA, noncompetitively, selectively, and reversibly inhibits inosine monophosphate dehydrogenase (IMPDH). IMPDH converts inosine monophosphate (IMP) to xanthine monophosphate (XMP), an intermediate metabolite in the production of guanosine triphosphate (GTP). GTP is needed for ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and protein synthesis. Therefore, MMF depletes the *de-novo* synthesis of guanosine nucleotides, impairing RNA, DNA, and protein synthesis. Supplementation of guanosine or deoxyguanosine has been shown to rescue lymphocytes from the cytostatic effects of MMF.[17]

What is unique about the mechanism of action of mycophenolate mofetil, which results in lymphocyte-specific effects?

Purine base synthesis may also be completed via the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) salvage pathway. However, as lymphocytes lack this salvage pathway, MMF more selectively inhibits lymphocyte proliferation and antibody formation.[8] Moreover, MMF preferentially blocks the type II isoform of IMPDH, predominantly located within lymphocytes, thus adding to a selectivity advantage with this immunosuppressive agent.[17]

How does mycophenolate mofetil induce anti-inflammatory effects?

MMF inhibits the recruitment of leukocytes into foci of inflammation by decreasing lymphocyte and monocyte adhesion to endothelial cells. MMF achieves this by preventing the glycosylation of lymphocyte and monocyte glycoproteins that are involved in adhesion to endothelial cells.[17]

What are the FDA-approved indications of mycophenolate mofetil and the suggested dosages?

MMF was approved by the FDA in 1995 for the prophylaxis of allograft rejection after renal transplantation. The recommended dose for this indication is 1g orally twice daily. One of the most studied systemic approaches to prophylaxis of renal allograft rejection is the combination of MMF and tacrolimus. Evidence based on randomized, controlled trials indicated that this combination is associated with the lowest rate of graft rejection and the highest rate of patient survival as compared to MMF in combination with cyclosporin (CsA), sirolimus, or everolimus.[18–20] MMF is also approved, in combination with CsA and systemic corticosteroids, for the prevention of acute allograft rejection after cardiac transplantation. The recommended dose for this indication is 1.5g orally twice daily. In 2000, the FDA approved MMF for the prophylaxis of acute rejection after liver transplantation. The recommended dose for this indication is 1g intravenously (IV) twice daily or 1.5g orally twice daily.

What information is available on other uses of mycophenolate mofetil in organ transplant recipients?

Simultaneous pancreas/kidney transplant. A recent study compared azathioprine (AZAT) to MMF in patients with simultaneous pancreas/kidney transplantation.[22] Unlike initial studies where no significant difference in the rate of acute rejection was observed, a more recent study showed MMF to be more effective than AZAT in preventing acute renal rejection after simultaneous transplantation.[21,22]

Lung transplant. MMF has also been administered in lung transplant patients as monotherapy and was able to exhibit a decreased rate of acute rejection compared to other immunosuppressants.[23,24] A study comparing MMF to AZAT, both in combination with CsA and prednisone, demonstrated that MMF was more effective in preventing bronchiolitis obliterans syndrome, a major cause of morbidity and mortality following lung transplantation.[25]

Lupus glomerulonephritis. Lupus glomerulonephritis (lupus nephritis) is a common manifestation of systemic lupus erythematosus (SLE) and is a strong predictor of poor overall outcome in patients with SLE.[26] A meta-analysis of MMF in lupus nephritis provided clinicians with a rational guide for the use of MMF, with a comparative evaluation showing that MMF was at least noninferior to cyclophosphamide.[27,28] In a long-term, follow-up study comparing MMF to AZAT, no significant differences were reported overall between the two agents; however, fewer opportunistic infections were reported in MMF-treated patients.[29] Two randomized studies comparing the combination of MMF and prednisone versus cyclophosphamide and prednisone yielded a high rate of clinical response in patients treated with MMF and prednisone.[30,31] Moreover, in a subset of refractory patients, MMF was able to achieve total remission in 9 of the 13 patients treated.[32]

What data are available on the off-label use of mycophenolate mofetil in the treatment of psoriasis?

As noted earlier, MPA

demonstrated therapeutic efficacy in psoriasis in the 1970s. As such, MMF use for psoriasis was attempted.[33] The first published use of MMF for psoriasis was in 1998 in an elderly gentleman who had chronic psoriasis vulgaris. He was successfully treated with MMF without any major side effects.[34] The Psoriasis Area and Severity Index (PASI) score in this patient decreased from 22.0 to 11.4 over five weeks with use of MMF 1g orally twice daily as monotherapy.[34]

Multiple case reports have demonstrated that MMF is an effective treatment option for psoriasis.[34–38] Change in the PASI score was also used to measure efficacy in a study of 11 patients with stable plaque-type psoriasis who received MMF 1g orally twice daily for three weeks followed by 0.5g twice daily.[39] Within three weeks, there was a reduction in PASI score of 40 to 70 percent in 7 of the 11 patients. Only one patient achieved a reduction in PASI of less than 25 percent from baseline. After six weeks, further improvement was noted in six patients.

How does mycophenolate mofetil compare with other oral systemic agents used to treat psoriasis?

Comparison to methotrexate. The efficacy and safety of MMF was compared to methotrexate (MTX) in one study for the treatment of chronic plaque psoriasis, revealing no significant differences in efficacy between these two agents.[40] In this study, 38 patients with PASI >10 were randomly assigned either MMF (n=15) or MTX (n=15) for 12 weeks. The PASI score decreased from 17.43 +/-7.42 at baseline to 3.97 +/-5.95 at end of treatment (EOT) among patients treated with MMF (p>0.05), whereas the PASI score decreased from 16.46 +/-5.29 at baseline to 3.17 +/-2.35 at EOT among those treated with MTX. The subjects were followed for 12 additional weeks after discontinuation of therapy with MMF or MTX, with the MMF-treated group showing PASI scores of 5.94 +/-4.27 and the MTX-treated group showing PASI scores of 4.77 +/-3.52 (p>0.05).[40] This study demonstrated no significant differences in efficacy between MMF and MTX, supporting the use of MMF for the treatment of psoriasis in patients unable to take MTX due to contraindication or toxicity.

Comparison to cyclosporin. MMF may serve as a viable alternative to CsA in some patients with psoriasis, especially those with, or predisposed to, renal dysfunction. The most significant forms of nephrotoxicity associated with CsA therapy are reversible impairment of glomerular filtration and irreversible interstitial fibrosis.[41] The latter problem occurs in some patients who are on CsA therapy for 6 to 12 months, representing an important factor that may restrict chronic use. A randomized, comparison study of MMF with CsA for the treatment of chronic plaque-type psoriasis was conducted where patients with psoriasis (N=54) were randomly assigned to treatment with either CsA or MMF for 12 weeks. This trial showed no difference in time to relapse of psoriasis between the two groups.[41] The mean PASI score decreased from 24.6 +/-11.1 to 6.6 +/-7.3 in the CsA-treated group and from 22.4 +/-9.2 to 10.6 +/-6.7 in MMF-treated group.[41] Although disease control was moderately compromised when compared to CsA, MMF may serve as an alternative option for patients with psoriasis who have renal impairment or in those who have experienced CsA-induced nephrotoxicity.[41]

What are some other off-label dermatological uses of mycophenolate mofetil and how successful has its efficacy been demonstrated in literature?

Immunobullous diseases. The major immunobullous diseases include pemphigus vulgaris, bullous pemphigoid, pemphigus foliaceus, epidermolysis bullosa acquisita, cicatricial pemphigoid, and paraneoplastic pemphigus. These disorders are characterized by formation of blisters and erosions in skin and/or mucous membrane, are often moderate to severe in intensity, and usually require systemic immunosuppressive therapy for adequate disease control. There have been several reports indicating the benefits of using MMF either as an adjunct or as monotherapy.[42–56] Nearly all of these reports conclude that MMF is a well-tolerated and effective corticosteroid-sparing agent in many bullous diseases.[33] Randomized, controlled trials of any intervention in pemphigus vulgaris or pemphigus foliaceus were examined, identifying 11 studies inclusive of 404 participants.[57] This review evaluating interventions for pemphigus vulgaris and pemphigus foliaceus found that MMF appears to be more effective than AZAT in controlling disease, although no difference was seen in maintenance of remission. Several other studies suggest that marked or complete remission is achieved more frequently with the use of MMF as compared to AZAT, with less potential for hepatotoxicity.[42–55]

Atopic dermatitis. Among the various types of eczematous dermatitis, MMF has been used most notably for atopic dermatitis (AD). The overall consensus among researchers supports the use of MMF in treating moderate-to-severe cases of AD, either as monotherapy or as an

adjunct in combination with topical corticosteroid treatment.[33] In a pilot study of 10 patients with severe refractory AD, patients received an increased dose of MMF at 2g/day orally to yield 68-percent improvement over a duration of 12 weeks.[58] The Scoring of Atopic Dermatitis (SCORAD) scale was used in this report to assess the severity of AD. The SCORAD scale was also used in another small study of 10 patients with moderate-to-severe AD who were given MMF 2g/day orally for one month and tapered to 1g/day.[59] Over a 20-week, follow-up period, there was a 74-percent reduction in the SCORAD as compared to baseline ($p<0.01$).

Other forms of dermatitis. Although there is limited data, chronic actinic dermatitis and dyshidrotic eczematous dermatitis (pompholyx) have also responded to MMF therapy.[60–62]

Connective tissue disorders. Of the connective tissue disorders, lupus erythematosus (LE) and dermatomyositis have received the most attention regarding off-label use of MMF. As discussed above, MMF has proven to be successful in patients with lupus nephritis. However, there are fewer well-designed studies or reports evaluating the use of MMF for cutaneous LE. Results from case reports and nonrandomized clinical trials suggest that MMF is effective in the treatment of skin manifestations of systemic LE.[33] There are also reports indicating successful use of MMF in two severe cases of resistant palmoplantar discoid LE, subacute cutaneous lupus erythematosus (SCLE), and chilblain lupus.[63–65]

Dermatomyositis. Publications evaluating the role of MMF for skin manifestations of dermatomyositis are limited. One report highlighted success with use of MMF for dermatological manifestations of dermatomyositis, noting control of cutaneous disease as a corticosteroid-sparing agent.[66] Other case reports also suggest improvement of cutaneous signs of dermatomyositis with MMF.[67–69]

Other reported uses. Other reported dermatological uses of MMF include graft-versus-host disease, cutaneous vasculitis, scleroderma, recurrent erythema multiforme, erythema nodosum, lichen planus, cutaneous Crohn's disease, sarcoidosis, and pyoderma gangrenosum.[70–82] MMF may be particularly beneficial for pyoderma gangrenosum when used in combination with other topical or systemic medications.[83]

What are the common adverse effects of mycophenolate mofetil and is there a dose-dependent relationship?

MMF is generally well-tolerated at usual doses, especially when compared to other systemic immunosuppressive agents, such as MTX, AZAT, and CsA. As compared to MTX and AZAT, MMF demonstrates less potential for hepatotoxicity, and unlike CsA, is not typically associated with nephrotoxicity. Therefore, depending on the clinical scenario, disease state involved, and other co-morbidities, MMF may offer a therapeutic advantage over other systemic immunosuppressive drugs from a risk-versus-benefit perspective.[33,40,41]

The most commonly reported side effects of MMF are GI-related, including nausea, vomiting, diarrhea, abdominal cramps, constipation, soft stools, and frequent stools.[47,84] Rare GI side effects have also been identified and include gastrointestinal hemorrhage, oral ulcerations, esophagitis, gastritis, duodenitis, villous atrophy, and ischemic colitis.[85–87] MMF-associated GI side effects are dose dependent and occur in up to 20 percent of patients at doses of 2g daily orally.[47,84] Genitourinary symptoms, such as frequency, urgency, dysuria, hematuria, and, occasionally, sterile pyuria, and urinary tract infection, may also occur with use of MMF.[88,89]

Hematological side effects, such as leukopenia, anemia, and thrombocytopenia, are relatively uncommon, observed in fewer than five percent of patients treated with MMF. Fortunately, hematological changes associated with the administration of MMF are usually mild, dose related, and reversible with discontinuation of therapy or dose reduction.[81,90] Importantly, higher doses of MMF are associated with an increased risk of leucopenia, reported to occur in up to 34.5 percent of patients treated with 3g daily.[14]

Adverse events reported in fewer than 20 percent of patients treated with 2 to 3g daily of MMF for the prevention of allograft rejection include fever, chest pain, dyspnea, cough, pharyngitis, bronchitis, pneumonia, tremor, dizziness, dyspepsia, back pain, peripheral edema, acneiform eruption, "rash," hypercholesterolemia, hypophosphatemia, hypokalemia, hyperkalemia, hyperglycemia, and renal function abnormalities.[14]

What is important for the clinician to keep in mind when addressing opportunistic infections in patients treated with mycophenolate mofetil?

As with other systemic immunosuppressive agents, predisposition to infection is an important caution in patients treated with MMF. An increased incidence of

opportunistic infections has been reported in patients treated with MMF, especially when exceeding doses of 2g daily.[82,91] Opportunistic infections are reported to occur in 40 percent or less of organ transplant recipients treated with MMF; however, the majority of cases were noted in patients simultaneously treated with other immunosuppressive agents.[89] Reported infectious complications in organ transplant recipients treated with MMF include herpes simplex infection, herpes zoster, human herpes virus type 6, human papillomavirus infection, aspergillosis, cryptococcosis, candidiasis, mucormycosis, cytomegalovirus, *Pneumocystis carinii* pneumonia, and pediatric disseminated varicella.[8,89,92–94] Clinical evaluation for signs of infection and periodic monitoring of complete blood cell (CBC) count are suggested as important components of follow up in patients treated with MMF.

What information is available on the risk of malignancy associated with use of mycophenolate mofetil? Does the relative risk potential differ among the transplant patient population and the dermatological patient population?

Malignancy potential associated with the use of MMF is a relevant concern, as with essentially any systemic immunosuppressive agent. In animal studies, MMF has not been shown to be carcinogenic; however, the risk of malignancy in humans is thought to be related to duration and intensity of immunosuppression.[14] One study showed that lymphoma or lymphoproliferative disease developed in 0.4 to 1 percent of patients receiving MMF, along with other immunosuppressive agents, for cardiac, renal, and hepatic transplantation. In addition, this study also showed nonmelanoma skin cancer developed in 1.6 to 4.2 percent of patients receiving MMF, along with other immunosuppressive agents, for cardiac, renal, and hepatic transplantation.[8]

Malignancy associated with use of MMF is mostly reported in the organ transplant population, where this agent is frequently used in combination with other systemic immunosuppressive agents. As such, it is difficult to accurately "tease out" risk associated with MMF use alone. It appears that the relative risk of malignancy development in organ transplant recipients, and likely other populations, is related more to the overall cumulative immunosuppressive effect rather than to one specific agent, especially as combination therapy is very commonly used in order to optimally sustain the viability of the transplanted organ.[33]

In the dermatological literature, few malignancies have been reported in patients treated with MMF or its pro-drug, MPA.[33] It is believed that for most dermatological uses, the level of immunosuppression with MMF is generally less than in the organ transplant population, as the daily dose of MMF is often lower, and monotherapy use of MMF is more common.

What absolute and relative contraindications does mycophenolate mofetil therapy pose?

Absolute contraindications of MMF are pregnancy and drug allergy. Increased risks of fetal loss and teratogenic effects have been noted in pregnant women receiving MMF, with the FDA changing the Pregnancy Category of MMF from C to D in October 2007. This change signifies that there is "evidence of human fetal risk, though the drug's potential benefits in pregnant women may outweigh that risk."[95] It is recommended that a negative serum pregnancy test be confirmed within one week before initiating therapy, and two forms of effective contraception be used before, during, and at least six weeks after discontinuation of MMF. Patients who have experienced allergic reactions to MMF should avoid use of the drug.

Relative contraindications to MMF include lactation, peptic ulcer disease, hepatic disease, and cardiopulmonary disease.[96] It has also been suggested that MMF not be used concurrently with AZAT as both have the potential to cause bone marrow suppression, including by different mechanisms.[14] At the time of the literature search and writing of this article, the authors found no studies evaluating concomitant administration of MMF and AZAT.

What are the suggested dosing recommendations with off-label use of mycophenolate mofetil for dermatological indications?

The dosing recommendations published in the manufacturer product monograph are for the use of MMF in renal, cardiac, and liver transplant patients. Because the dermatological uses of MMF are off-label, there are no firm published dosing recommendations. However, based on published literature in adults, the usual dose of MMF ranges from 2 to 3g per day orally.[97,98] The typical starting dose is 1 to 2g per day, usually divided over twice-daily dosing. If no improvement is noted after one month of therapy, it is suggested that the dose be increased by 500mg increments up to 3g per day.[33]

Patients with renal impairment. In adult patients with chronic renal insufficiency with a glomerular filtration rate <25mL/min, it is suggested that the daily dose should not exceed 1g twice daily.[14]

Pediatric patients. In the pediatric population, MMF administration at 600mg/m^2 daily is recommended, however in treating pediatric patients for autoimmune disease, a slightly higher dose of 900mg/m^2 has been reported.[97]

What guidelines are available for clinicians to better monitor patients receiving mycophenolate mofetil therapy?

Laboratory monitoring guidelines with use of MMF recommended by the manufacturer in the approved product labeling (package insert) include a baseline CBC with differential and platelet count, followed by continued monitoring of the aforementioned two parameters weekly for the first month, bi-weekly for the second and third months, and monthly thereafter through the first year of treatment.[14] Current literature suggests a baseline CBC with differential and platelet count and a chemistry profile with inclusion of liver and renal function tests, with only the CBC with differential continued following the same schedule recommended by the product package insert.[96] With no firm monitoring guidelines developed with use of MMF for dermatological indications, it is prudent to obtain baseline laboratory testing in order to better monitor for potential adverse reactions. Baseline testing should include a CBC with differential and platelet count and chemistry profile with inclusion of liver and renal function tests. Follow-up testing of hematological parameters is also prudent as discussed earlier. Importantly, reduction of the dose of MMF with repeat CBC with differential testing, or discontinuation of MMF therapy, is warranted when the white blood count drops below 3,500 to 4,000cells/mm^3.[96]

What are some of the significant drug interactions associated with mycophenolate mofetil?

Drugs that interact with MMF can be classified into the following three categories: (1) those that increase the serum level of MMF, (2) those that decrease the serum level of MMF, and (3) those in which MMF reduces the serum level of a concomitantly administered drug. Medications that can increase the serum level of MMF include salicylates and probenecid.[8,14] Therefore, it may be necessary to lower the dose of MMF with continuous coadministration in order to avoid an unanticipated higher level of immunosuppression, posing an increased potential for adverse reactions. Medications that can decrease the serum level of MMF include simultaneous intake with rifampin,[99] fluoroquinolones, metronidazole, glucocorticosteroids, CsA, cholestyramine, antacids, iron, sevelamer, and calcium polycarbophil.[8,14,99–104] Lastly, some medications, when taken in combination with MMF, may exhibit a decrease in serum level. This has been noted with the antiretroviral agent, nevirapine. However, similar interaction with other antiretroviral drugs coadministered with MMF have not been reported to date.[105]

What summary statements apply to the use of mycophenolate mofetil in dermatology?

MMF is a unique immunosuppressive agent, exhibiting a somewhat "selective" mechanism of action that differs from other systemic immunosuppressive agents. Its availability as an oral agent makes it amenable to use in the ambulatory setting. Most of the experience with MMF is based on use in organ transplant recipients. However, more reports of successful experience are being captured and published for "off label" dermatological indications, including use in patients with psoriasis, AD, immunobullous disorders, and connective tissue diseases. Overall, MMF offers a superior safety profile as compared to many other systemic immuonosuppressive agents, such as MTX, AZAT, and CsA. Nevertheless, the potential adverse reactions associated with MMF therapy are to be respected, including predominantly GI side effects, hematological reactions, and increased predisposition to infection. Appropriate baseline evaluation and testing coupled with periodic monitoring are warranted. More cautious use is recommended in patients with renal impairment. The risk of malignancy associated with use of MMF as a systemic monotherapy immunosuppressive agent is not known, especially in the "dermatological use" patient population.

With continued experience, dermatologists will better identify the relative efficacy and safety of MMF as compared to other systemic immunosuppressive agents for specific cutaneous disease states. This will allow clinicians to more optimally address with patients the risk-versus-benefit profile of MMF as compared to other systemic agents. As for now, available data supports MMF as a viable therapeutic option for many dermatological disorders requiring use of a systemic immunosuppressive agent.

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